SPECIAL ARTICLE

Management of childhood lead poisoning

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CHELATION TREATMENT for childhood lead poisoning may be life-saving and decreases the body burden of lead far more rapidly than normal excretory processes can.[1] Furthermore, chelating agents markedly enhance removal of that fraction of body lead that is readily mobile and considered to be the most toxic.[1-6] However, lead poisoning is a wholly preventable disorder caused by the wide dissemination of lead into the environment.[7,8] Medical treatment with chelating agents must not be considered a substitute for dedicated preventive efforts to eradicate controllable sources of lead (e.g., substandard housing that contains lead-bearing paints, combustion of leaded gasoline). Although repeated courses of chelation therapy may be necessary for medical reasons, the source(s) of environmental lead must be identified and removed for preventive reasons.

This review is based on our experience in four different lead poisoning treatment clinics and reflects our consensus on current management criteria.

PHARMACOLOGIC CONSIDERATIONS

Lead poisoning is treated with drugs capable of binding (chelating) lead and of enhancing its excretion. These

drugs deplete the soft tissues of lead and may thus reduce its acute toxicity. They are also used, in asymptomatic children, to reduce a potentially dangerous body burden of lead. All drugs are used to enhance the slow process of natural lead excretion. All drugs have potential side effects and should be used carefully. A brief description of the essential pharmacologic aspects of the various drugs follows. Detailed guidelines for specific situations are given in the next section.

BAL

Mechanism of action. Two molecules of BAL combine with one atom of heavy metal to form a stable complex. BAL enhances fecal as well as urinary excretion of lead and diffuses well into erythrocytes. It can be administered in the presence of renal impairment because it is predominantly excreted in bile.[1]

BAL	(British anti-lewisite) Dimercaptopropanol
CaNa$_2$-EDTA	Disodium calcium–edetate
EP	Erythrocyte protoporphyrin
G-6-PD	Glucose-6-phosphate dehydrogenase

Route of administration and dosage. BAL is available only in oil for intramuscular administration. It must be given every 4 hours. Dosages are discussed below.

Toxicity. Mild febrile reactions may occur, and transient elevation of hepatic transaminase activities may be observed. Other minor adverse effects include, in order of frequency, nausea and occasional vomiting, headache, mild conjunctivitis, lacrimation, rhinorrhea, and salivation. Most side effects are transient and rapidly subside as the drug is metabolized and excreted.

Precautions. In patients with G-6-PD deficiency, BAL should be used only in life-threatening situations, because it may induce hemolysis. Medicinal iron should never be administered during BAL therapy, because the combination is very toxic. If iron deficiency coexists, its management should be postponed until BAL therapy is concluded. In cases of extreme anemia blood transfusions are preferable.

CaNa$_2$-EDTA[9-16]

Only CaNa$_2$-EDTA (calcium disodium versenate) should be used for treatment of lead poisoning. Na$_2$-EDTA (endrate disodium) should never be used for treatment of lead poisoning, because it may induce fatal hypocalcemia and tetany.

Mechanism of action. CaNa$_2$-EDTA increases urinary lead excretion 20- to 50-fold. CaNa$_2$-EDTA does not enter the cells; thus it removes lead from the extracellular compartment. Indirectly, lead is reduced in the soft tissue, central nervous system, and red blood cells.[1]

Route of administration and dosage. CaNa$_2$-EDTA may be given intravenously or intramuscularly. The preferred and most effective route is a continuous intravenous infusion; a given dose is most effective if infused over 6 hours.[10] CaNa$_2$-EDTA should be diluted to a concentration <0.5% in dextrose and water or 0.9% saline solution. When administered intravenously as a single dose, it should be similarly diluted and administered by slow infusion over 15 to 20 minutes. Intramuscular administration of CaNa$_2$-EDTA is extremely painful and should be given with procaine (0.5%) by deep injection.

CaNa$_2$-EDTA should not be given orally, because it may enhance absorption of lead from the gastrointestinal tract.

Dosages vary in different situations and are discussed below. In all cases, courses should be limited to 5 days, followed by at least 2- to 5-day intervals to allow recovery from zinc depletion.

Toxicity. The kidney is the principal site of toxicity. Renal toxicity is dose related, reversible, and rarely occurs at doses <1500 mg/m^2. The renal toxicity may be reduced by assuring adequate diuresis. CaNa$_2$-EDTA should never be given in the absence of an adequate urine flow. Before administering it intramuscularly in children in good clinical condition, adequate oral intake of fluids must be assured.

Precautions. During chelation with CaNa$_2$-EDTA, urine and its sediment, BUN, serum creatinine, and liver function tests must be carefully monitored. The appearance of protein and formed elements in urinary sediment, and rising BUN and serum creatinine values signify impending renal failure, the serious toxicity associated with excessive or prolonged administration of EDTA. Inasmuch as CaNa$_2$-EDTA may deplete zinc stores and cellular injury may be associated with zinc depletion, CaNa$_2$-EDTA should be used with great caution.

CaNa$_2$-EDTA, used alone without concomitant BAL therapy, may aggravate symptoms in patients with very high blood lead levels. Thus it should be used exclusively in conjunction with BAL when the blood lead level is >70 µg/dl or clinical symptoms consistent with lead poisoning are present. In such cases the first dose of BAL should always precede the first dose of CaNa$_2$-EDTA by at least 4 hours.

D-Penicillamine. D-Penicillamine is not licensed by the Food and Drug Administration for the treatment of lead poisoning. Its use for this indication is thus to be considered experimental. It is the only commercially available oral chelating agent. It can be given over a long period (days). Toxic side effects may occur in as many as 20% of patients given the drug.[17]

Mechanism of action. D-Penicillamine enhances urinary excretion of lead, although not as effectively as CaNa$_2$-EDTA. Its specific mechanism of action is not well understood.

Route of administration and dosage. D-Penicillamine is administered orally. It is currently available in capsules (125 and 250 mg). These capsules may be opened and suspended in liquid, if necessary. The usual dose is 30 mg/kg. Side effects can be minimized by initiating therapy with small doses, for example, 25% of the desired final dose, increased after 1 week to 50% and again after 1 week to the full dose, while monitoring for possible toxicity.

Toxicity. The main side effects of D-penicillamine are reactions resembling those of penicillin sensitivity, including fevers, rashes, leukopenia, thrombocytopenia, and eosinophilia. Rarely, more severe and even life-threatening reactions (autoimmune hemolytic anemia, Stevens-Johnson syndrome) have been observed. Anorexia, nausea, and vomiting are infrequent. Of most concern, however, are isolated reports of nephrotoxicity, possibly from hypersensitivity reactions. For these reasons, patients should be carefully and frequently monitored for clinically obvious side effects, and frequent blood counts, urinalysis, and renal function tests should be performed. In particular, blood counts and urinalysis should be done twice weekly, at least in the first 3 weeks of treatment. If the absolute neutrophil count falls to <1500/µl it should be immediately rechecked, and treatment should be stopped if it falls to <1200/µl. D-Penicillamine should therefore not be given on an outpatient basis if there is any question about compliance with appointments.

D-Penicillamine should not be administered in patients with known penicillin allergy.

New agents. Dimercaptosuccinic acid and 2-3-dimercapto-propane-1-sulphonate are both water-soluble derivatives of BAL. Although both appear promising and safe and have been used successfully in treatment of other heavy-metal poisoning, these drugs are presently in the investigative stage for the treatment of lead poisoning.[18, 19]

ACUTE LEAD ENCEPHALOPATHY

Acute lead encephalopathy is characterized clinically by some or all of the following symptoms: coma, seizures, bizarre behavior, ataxia, apathy, incoordination, vomiting, alteration in the state of consciousness, and subtle loss of recently acquired skills. Any one or a matrix of these symptoms associated with an elevated blood lead concentration constitutes an acute medical emergency. Lead encephalopathy is almost always associated with a blood lead concentration >100 μg/dl, although it has been reported at blood lead levels as low as 70 μg/dl.[1,4]

General supportive management. All oral intake is prohibited initially until the child's condition has significantly improved. Parenteral fluid therapy is begun immediately; volume is restricted to basal requirements plus a careful assessment of continuing losses. Excessive intravenous fluid administration must be avoided. Once urine flow is established by administering dextrose in water (10 to 20 ml/kg body weight), chelation treatment, already begun with BAL alone for one dose, is continued with simultaneous administration of CaNa$_2$-EDTA. An adequate flow of urine must be established before intravenous chelation therapy. Parenteral fluid therapy minimizes vomiting that may accompany administration of BAL and ensures prompt excretion of CaNa$_2$-EDTA, a drug excreted exclusively by the kidney. For initial control of seizures, diazepam or paraldehyde is the preferred drug. Barbiturate and phenytoin are reserved for the long-term management of recurring seizures, only after the acute episode is managed and consciousness has been fully recovered. Although it is desirable to evacuate any residual lead from the bowel, this should not delay the start of chelation therapy. Surgical decompression and hypertonic solutions to relieve intracranial pressure and cerebral edema are contraindicated.

The diagnosis of acute lead encephalopathy can usually be made without lumbar puncture, which is extremely risky because of the presence of increased intracranial pressure. In fulminant lead encephalopathy, increased intracranial pressure may be present in the absence of any of the usual preliminary signs (changes in blood pressure, pulse or respiration, retinal hemorrhage or edema). If examination of the CSF is absolutely essential for the differential diagnosis, the very least amount of fluid, not exceeding a few drops, should be carefully obtained.

Chelation therapy. Treatment is begun with a priming dose of 75 mg/m^2 BAL only, given by deep intramuscular injection; BAL is administered at a dose of 450 mg/m^2/24 hours, in divided doses of 75 mg/m^2 every 4 hours. Once the priming dose is given and an adequate urine flow is established, administration of CaNa$_2$-EDTA is begun at a

dose of 1500 mg/m^2/24 hours. CaNa$_2$-EDTA is given by continuous intravenous drip in dextrose and water or 0.9% saline solution. The concentration of CaNa$_2$-EDTA should not exceed 0.5% in the parenteral fluid. (In the treatment of acute encephalopathy, restriction of parenteral fluids takes precedence, so that CaNa$_2$-EDTA may have to be given intramuscularly if fluid overload is to be avoided.) Combined BAL–CaNa$_2$-EDTA therapy is given for a total of 5 days. During treatment, renal and hepatic function and serum electrolyte levels should be monitored daily.

A second course of chelation therapy with CaNa$_2$-EDTA alone or with BAL, depending on the blood lead concentration, may be required after a 2-day interval. A third course is required only if the blood lead concentration rebounds to a value $\geq$50 μg/dl within 48 hours after treatment. Unless there are compelling clinical reasons, it is desirable to wait at least 5 to 7 days before beginning a third course of CaNa$_2$-EDTA.

SYMPTOMATIC LEAD POISONING WITHOUT ENCEPHALOPATHY

Symptomatic lead poisoning without encephalopathy is characterized by one or several of the following symptoms: decrease in play activity, lethargy, anorexia, sporadic vomiting, intermittent abdominal pain, and constipation. Symptomatic lead poisoning is usually associated with a blood lead concentration >70 μg/dl, although occasionally may be associated with a blood lead concentration as low as 50 μg/dl. *If the blood lead concentration is <50 μg/dl, other diagnostic possibilities should be vigorously sought.* Because all symptomatic children potentially have acute lead encephalopathy, treatment and supportive measures must be instituted immediately on an emergency basis.[1,4]

General supportive management. All oral intake is prohibited and the guidelines of parenteral fluid therapy are followed as noted above for the treatment of lead encephalopathy. Intravenous fluids are given at a rate consistent with basal requirements plus ongoing losses. Excessive fluid administration must be avoided.

Chelation therapy. Treatment is begun with a priming dose of 50 mg/m^2 BAL by deep intramuscular injection; BAL is administered at a dose of 300 mg/m^2/24 hours in divided doses of 50 mg/m^2 every 4 hours. Once the priming dose is given and an adequate urine flow is established, administration of CaNa$_2$-EDTA is begun at a dose of 1000 mg/m^2/24 hours. CaNa$_2$-EDTA is given by continuous intravenous drip in dextrose and water or 0.9% saline solution. Although continuous infusion of CaNa$_2$-EDTA is preferable, it may be replaced by doses of 175 mg/m^2 every

4 hours, given either intravenously over 15 to 20 minutes through a heparin lock or by deep intramuscular injection mixed with procaine. The concentration of $CaNa_2$-EDTA should not exceed 0.5% in the parenteral fluid. Combined BAL=$CaNa_2$-EDTA therapy is given for a total of 5 days.

During treatment, renal and hepatic function and serum electrolyte levels should be monitored daily. It is advisable to measure the blood lead concentration daily. (It will be necessary to interrupt the $CaNa_2$-EDTA infusion for 1 hour before this sample is obtained, to avoid a spuriously high value). If the blood lead concentration reaches ≤50 μg/dl, as it may within 3 days of combined BAL–$CaNa_2$-EDTA therapy, BAL may be safely discontinued and $CaNa_2$-EDTA continued for a full 5-day course of treatment. If measurements of blood lead cannot be obtained in time, it is safe to continue BAL for the full 5-day course. Except under highly unusual circumstances, $CaNa_2$-EDTA should not be administered for more than 5 consecutive days.

A second course of chelation therapy may be required after a 2- to 4-day interval, to be started with $CaNa_2$-EDTA alone or with concomitant BAL, depending on the blood lead concentration. A third course may be required if the blood lead concentration rebounds to a value ≥50 μg/dl within 7 to 10 days after treatment. Unless there are compelling clinical reasons, it is highly desirable to allow 5 to 7 days before beginning a third course of $CaNa_2$-EDTA.

ASYMPTOMATIC CHILDREN WITH INCREASED BODY BURDEN OF LEAD

Although children with increased body burden of lead are clinically asymptomatic, it is likely that they have pervasive metabolic effects involving heme synthesis,[20-23] red cell nucleotide metabolism,[24] vitamin D and cortisol metabolism[25-27] and renal function,[1, 4] and subclinical neurobehavioral effects.[28-31] Some of these profound metabolic and cellular effects of lead have been observed at blood lead concentrations <25 μg/dl.[20, 24, 26, 30, 31]

Diagnostic assessment. In asymptomatic children it is essential to have a firm diagnosis based on an elevated blood lead level before treatment is initiated. Measurements of blood lead concentration in capillary samples are subject to contamination and should never be the only basis for treatment. Treatment should be initiated only after a confirmatory measurement of the venous blood lead concentration. Even when there is strong additional evidence of lead poisoning, such as paint flakes in the abdomen or lead lines in the bones on x-ray examination, it is preferable to wait for a confirmatory measurement of venous blood lead. Although measurements of erythrocyte protoporphyrin may be helpful in evaluating overall toxicity,

blood lead measurement is the criterion on which to base a decision as to whether chelation therapy should be considered. (The EP may increase initially during chelation therapy.) Therapeutic decisions should also be based on the results of the $CaNa_2$-EDTA provocative test.

Chelation therapy

Blood lead concentration ≥*70* μg/dl. If the blood lead level is ≥70 μg/dl, BAL and $CaNa_2$-EDTA should be given, in the same doses and with the same guidelines as for treatment of symptomatic lead poisoning without encephalopathy.

A second course of chelation therapy with $CaNa_2$-EDTA alone may be required if the blood lead concentration rebounds to a value ≥50 μg/dl within 5 to 7 days after treatment. Unless there are compelling clinical reasons, it is highly desirable to allow at least 5 to 7 days before beginning a second course of $CaNa_2$-EDTA.

Blood lead concentration 56 to 69 μg/dl. If the blood lead value is between 56 and 69 μg/dl, treatment should be limited to $CaNa_2$-EDTA only.

$CaNa_2$-EDTA is given for 5 days at a dose of 1000 mg/m²/day, preferably by continuous infusion (or in divided doses intravenously as above). Alternatively, however, if environmental control of the lead hazards has been achieved, this treatment may be given on an outpatient basis, at a dose of 1000 mg/m²/day, preferably by intravenous infusion over 1 hour, with adequate hydration (250 ml/m²). As a least preferable option, $CaNa_2$-EDTA may be administered intramuscularly mixed with procaine, at the same single daily dose of 1000 mg/m² for 5 consecutive days. This route of administration may represent a painful but practical alternative, when circumstances dictate it.

During treatment, renal and hepatic function and serum electrolyte levels should be monitored. A blood lead concentration should be obtained at 72 hours of treatment (it will be necessary to interrupt the $CaNa_2$-EDTA infusion for 1 hour before this sample is obtained, to avoid a spuriously high value) to monitor the effectiveness of treatment.

$CaNa_2$-EDTA treatment should be continued for 5 days. Except under highly unusual circumstances, it should not be administered for more than 5 consecutive days.

A second course of chelation therapy, with $CaNa_2$-EDTA alone, may be required if the blood lead concentration rebounds to a value ≥50 μg/dl within 5 to 7 days after treatment. Unless there are compelling clinical reasons, it is highly desirable to allow a period of 5 to 7 days before beginning a second course of $CaNa_2$-EDTA.

Blood lead concentration 25 to 55 μg/dl. When the blood lead value is persistently between 25 and 55 μg/dl and accompanied by EP persistently >35 μg/dl, the decision to proceed with chelation therapy should be based

Table. Choice of chelation therapy based on symptoms and blood lead concentration

Clinical presentation	Treatment	Comments
Symptomatic children		
Acute encephalopathy		
	BAL 450 mg/m²/day	Start with BAL 75 mg/m² IM every 4 hours.
	CaNa₂-EDTA 1500 mg/m²/day	After 4 hours start continuous infusion of CaNa₂-EDTA 1500 mg/m²/day.
		Therapy with BAL and CaNa₂-EDTA should be continued for 5 days.
		Interrupt therapy for 2 days.
		Treat for 5 additional days, including BAL if blood Pb remains high.
		Other cycles may be needed depending on blood Pb rebound.
Other symptoms		
	BAL 300 mg/m²/day	Start with BAL 50 mg/m² IM every 4 hours.
	CaNa₂-EDTA 1000 mg/m²/day	After 4 hours start CaNa₂-EDTA 1000 mg/m²/day, preferably by continuous infusion, or in divided doses IV (through a heparin lock).
		Therapy with CaNa₂-EDTA should be continued for 5 days.
		BAL may be discontinued after 3 days if blood Pb <50 μg/dl.
		Interrupt therapy for 2 days.
		Treat for 5 additional days, including BAL if blood Pb remains high.
		Other cycles may be needed depending on blood Pb rebound.
Asymptomatic children		
Before treatment, measure venous blood lead.		
Blood Pb >70 μg/dl		
	BAL 300 mg/m²/day	Start with BAL 50 mg/m² IM every 4 hours.
	CaNa₂-EDTA 1000 mg/m²/day	After 4 hours start CaNa₂-EDTA 1000 mg/m²/day, preferably by continuous infusion, or in divided doses IV (through a heparin lock).
		Treatment with CaNa₂-EDTA should be continued for 5 days.
		BAL may be discontinued after 3 days if blood Pb <50 μg/dl.
		Other cycles may be needed depending on blood Pb rebound.
Blood Pb 56 to 69 μg/dl		
	CaNa₂-EDTA 1000 mg/m²/day	CaNa₂-EDTA for 5 days, preferably by continuous infusion, or in divided doses (through a heparin lock).
		Alternatively, if lead exposure is controlled, CaNa₂-EDTA may be given as a single daily outpatient dose IM or IV.
		Other cycles may be needed depending on blood Pb rebound.
Blood Pb 25 to 55 μg/dl		
Perform CaNa₂-EDTA provocation test to assess lead excretion ratio (see text).		
If ratio >0.70	CaNa₂-EDTA 1000 mg/m²/day	Treat for 5 days IV or IM, as above.
If ratio 0.60 to 0.69		
Age <3 years of age	CaNa₂-EDTA 1000 mg/m²/day	Treat for 3 days IV or IM, as above.
Age >3 years of age	No treatment	Repeat blood Pb and CaNa₂-EDTA provocation test periodically.
If ratio <0.60	No treatment	Repeat blood Pb and CaNa₂-EDTA provocation test periodically.

on positive findings of a carefully performed CaNa₂-EDTA provocation test. (It must again be emphasized that chelation therapy should complement, not replace, abatement of controllable lead sources.)

CaNa₂-EDTA PROVOCATION TEST. First, a repeated baseline blood lead level is obtained and the patient is asked to empty the bladder. Then CaNa₂-EDTA is administered at a dose of 500 mg/m² intravenously in 250 ml/m² of 5% dextrose, infused over 1 hour. (A painful but practical alternative is to administer the same dose intramuscularly mixed with procaine and to encourage the child to drink as much as possible in the first 2 hours). All urine must be collected with lead-free equipment over 8 hours. The urine volume should be carefully measured, and aliquots should be sent to the laboratory for measurement of the concentration of lead. Extreme care should be exercised to use only lead-free equipment. If this is not available in the clinic, it may be best that the entire urine volume be sent to
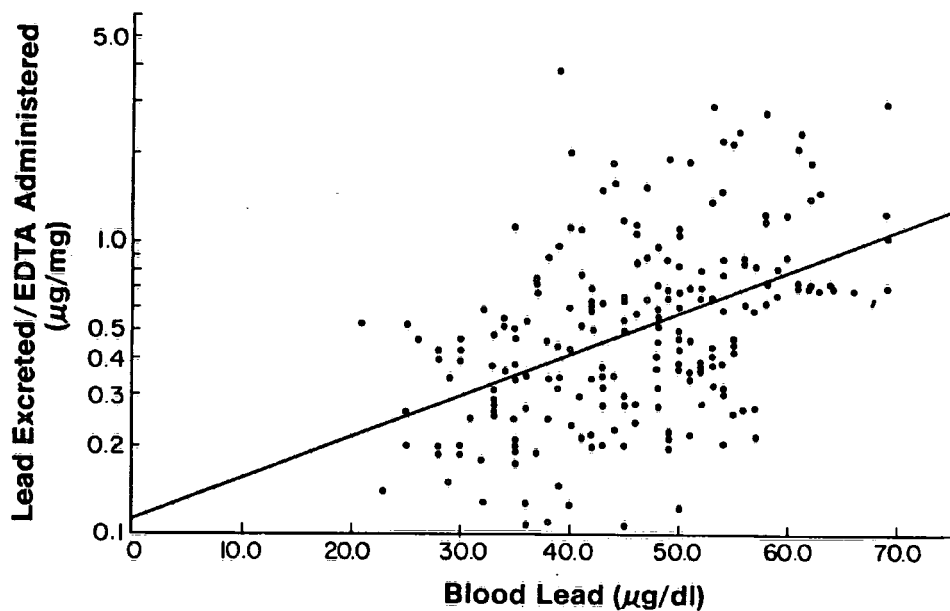
Figure. Lead excretion ratio as a function of blood lead. Data expressed as decimal logarithm of CaNa$_2$-EDTA excretion ratio (μg lead excreted/mg EDTA administered) versus blood lead. There is a significant correlation ($r = 0.466$, $P < 0.001$), with a slope of 0.014 and an intercept of -0.95.

Data shown were obtained by different techniques. At Columbia University, 77 children in an outpatient setting received CaNa$_2$-EDTA as a 20-minute intravenous infusion at a dose of 50 mg/kg, followed by 250 ml/m^2 5% dextrose over 1 hour; urine was collected for 7 to 8 hours. At Albert Einstein College of Medicine (Montefiore Hospital), 37 hospitalized children received CaNa$_2$-EDTA intramuscularly with procaine at a dose of 500 mg/m^2; urine was collected for 8 hours. At John Hopkins University School of Medicine, 50 hospitalized children received CaNa$_2$-EDTA intramuscularly at a dose of 25 mg/kg at 0 and 12 hours; urine was collected for 24 hours. At Children's Hospital Medical Center, 46 children in the outpatient clinic received CaNa$_2$-EDTA intramuscularly with procaine at a dose of 50 mg/kg; urine was collected for 6 to 7 hours. Despite these differences, slopes and intercept of regression lines were remarkably similar: excretion ratio makes the CaNa$_2$-EDTA provocation test independent of both the dose administered and the child's age and body weight. Therefore, data could be pooled together in a single regression line. Combined data represent, to the best of our knowledge, the largest series of CaNa$_2$-EDTA provocation tests in children.

a laboratory where the volume can be measured with lead-free equipment and aliquots for lead and creatinine measurements can be taken without contaminating the sample.

INTERPRETATION OF CaNa$_2$-EDTA PROVOCATION TEST. The concentration of lead in the urine (in micrograms per milliliter) is multiplied by the volume (in milliliters), to obtain the total excretion (in micrograms). The total urinary excretion of lead (micrograms) is divided by the amount of CaNa$_2$-EDTA given (milligrams) to obtain the "lead excretion ratio":

$$\frac{\text{Lead excreted } (\mu g)}{\text{CaNa}_2\text{-EDTA given (mg)}}$$

The CaNa$_2$-EDTA provocation test is considered positive if the lead excretion ratio exceeds 0.60.

The recommendations of the authors are based on their experience with 210 provocation tests[1,3,6,32,33] (Figure).

Inspection of the Figure shows that a ratio >0.60 is never obtained in 12 children with blood lead level <30 μg/dl, and is always obtained in 19 children with blood lead level >60 μg/dl. At blood lead level 30 to 39 μg/dl, the ratio is >0.60 in six (11.5%) of 52 children; at blood lead level 40 to 49 μg/dl the ratio is >0.60 in 25 (37.9%) of 66 children; and at blood level 50 to 59 μg/dl the ratio is >0.60 in 30 (49.2%) of 61 children.

It appears, therefore, that a ratio <0.60 represents an appropriate cutoff point to distinguish children with "markedly increased" excretion. (It is not possible to define a normal excretion range because no data are available and it would be unethical to obtain them in children with blood lead values <25 μg/dl. In addition, even the lower blood lead levels observed in children from industrialized countries are significantly higher than those in children from remote areas uncontaminated by lead, which most likely represent the truly normal blood lead level.[34] However, extrapolation from these data predicts, at

blood lead level 1 µg/dl, an excretion ratio of 0.1, six times lower than the proposed cutoff of 0.60).

GUIDELINES FOR TREATMENT BASED ON $CaNa_2$-EDTA PROVOCATION TEST. If the lead excretion ratio is >0.70, a 5-day course of $CaNa_2$-EDTA 1000 mg/m² intramuscularly or intravenously should be given, as above.

If the lead excretion ratio is between 0.60 and 0.69, (1) children younger than 3 years should receive treatment for 3 consecutive days with 1000 mg/m² $CaNa_2$-EDTA, as discussed above; and (2) in children older than 3 years the test should be repeated every 2 to 3 months and treatment started if the lead excretion ratio increases to >0.70 (in which case treatment shall consist of 3 days with 1000 mg/m² $CaNa_2$-EDTA, as above).

In children who have received chelation therapy, repeated cycles are indicated if the blood lead concentration rebounds to within 5 µg/dl of the original value, 7 to 10 days after treatment.

In all children, regardless of age, with elevated blood lead and EP values but with an excretion ratio <0.60, blood lead and EP should be monitored frequently. If the elevation of blood lead values persists, the $CaNa_2$-EDTA provocation test should be repeated periodically (every 2 to 3 months).

IMMEDIATE TREATMENT FOLLOW-UP

The goal of chelation therapy is to permanently reduce the blood lead level to <25 µg/dl and that of EP to <35 µg/dl. To achieve this goal it may be necessary to give several courses of treatment. It cannot be overemphasized, however, that repeated courses of therapy are counterproductive unless the source of lead has been identified and eradicated. Children receiving chelation therapy should not be released from the hospital until all lead hazards in their homes and elsewhere have been controlled and eliminated and, if necessary, suitable alternative housing has been arranged. With vigorous public health measures complete and safe abatement should be achieved during the treatment period.[8] If a child with elevated blood lead concentration cannot be moved to new housing, multiple repeated courses of $CaNa_2$-EDTA in a clinically asymptomatic child with stable blood lead values may be counterproductive; parents may despair at the ineffectiveness of therapy and fail to return to the clinic. It is more important in these unfortunate situations to maintain follow-up so that a rise in blood lead concentrations is detected promptly.

At the end of each treatment cycle the blood lead concentration usually declines to values <25 µg/dl. However, within a few days reequilibration takes place and results in a rebound; thus the blood lead level must be rechecked 7 to 10 days after the end of treatment.

If the blood lead level rebounds to within 5 µg/dl of the value before the last cycle, additional treatment cycles are indicated (unless the concentration after rebound is <25 µg/dl). A blood lead concentration that rebounds to above the pretreatment value is evidence of renewed and excessive intake.

If the blood lead level remains low, its measurement must be repeated, initially biweekly, then at monthly intervals, to assure that the decreased level is permanent.

Iron deficiency states, which may accompany lead poisoning, require therapeutic doses of iron in addition to the correction of other possible nutritional deficiencies.

LONG-TERM CLINICAL FOLLOW-UP AND MANAGEMENT

The vast majority of children with lead poisoning now referred to pediatricians from screening clinics are asymptomatic. Acute lead encephalopathy is rare. Lead poisoning (with or without clinical symptoms) should be reported to the local health authorities, who usually have prime responsibility for environmental investigation and abatement of lead hazards in the home or elsewhere.

Because lead has been widely disseminated into the environment, thereby providing multiple opportunities for repeated overexposure, lead poisoning should be managed as a chronic disorder. A team approach involving public health personnel, pediatrician, pediatric nurse practitioner, and social worker is likely to be the most effective. Commonly this can be accomplished best if children with lead poisoning are referred for long-term follow-up to a special clinic where all phases of clinical management can be coordinated and continuity of care is maintained.

At the outset, a long-term plan of management is developed. Age, the intensity of hand-to-mouth activity, pica, diet modification, environmental exposure, and serial laboratory data are taken into account. The objectives are to reduce the body burden of lead and to prevent recurrences. All preschool-aged housemates of index cases should be examined. All cases should be reported to social service for assistance in obtaining safe housing. Extended follow-up to at least 6 years of age is usually necessary.

Identification of lead source(s). In all cases, first priority is given to identification of important sources of excess lead in the child's environment and prompt separation of the child therefrom.[8] A thorough history can facilitate the identification and abatement of the most important sources of lead. Although this crucial part of therapy (abatement) is usually performed by health department personnel, not uncommonly information obtained in the clinic provides clues to unsuspected sources. The environmental history obtained in the clinic should include a list of all dwellings currently or recently visited by the child

(primary residence, homes of relatives and baby sitters, schools, daycare centers) and evaluation of each building's age and state of repair. In the United States a high proportion of buildings constructed prior to 1960 have lead-bearing paints and putty on both exterior and interior areas accessible to the child. Structures in poor repair often have lead-containing chips or pulverized fragments in the household dust. Play areas, especially urban playgrounds near vehicular traffic, dirt playgrounds and dirt yards, painted metal fences and walls, and vacant lots formerly containing lead-painted structures should be identified as potential lead sources. Occupational histories for all adults in various dwellings should be ascertained to learn if any are working in lead-related industries. Lead trades include, but are not limited to, secondary lead smelting (recovery of lead from old storage batteries), lead scrap smelting, storage battery manufacturing and repair, metal founding, ship breaking, automobile assembly and body and radiator repair, demolition of painted metal structures (such as bridges), and demolition and renovation of old houses and other structures. Adults who work in lead industries must shower before coming home and must leave all work clothes, including shoes, at the work place; these clothes must not be cleaned or washed at home. Thus lead-bearing dust from the place of employment will not contaminate the house. Additional sources may include old lead-painted cribs and beds and the burning of lead-painted wood in wood-burning stoves. Proximity to lead smelters, ingestion of lead-containing dust, and inhalation of lead from the combustion of gasoline contribute to the overall body burden of lead in children, but the high concentration of lead that ultimately results in clinical lead poisoning is most frequently associated with ingestion of lead-bearing paint. Uncommon causes of poisoning include ingestion and retention in the stomach of metallic lead (fishing weights, curtain weights, shot, jewelry painted with lead to simulate pearl), contamination of acidic foods and beverages from improperly lead-glazed ceramic pitchers, pots, and cups and from opened lead-soldered food cans, and the home burning of battery casings. Inhalation of fumes (sniffing) from small leaded-gasoline containers has occurred in older children. Poisoning has also been traced to oriental cosmetics (surma, a black eyeliner containing up to 85% lead) and to Mexican and Oriental folk remedies (azarcon, greta, paylooah).

Medical management during abatement of lead paint hazards. If the source of lead is limited to such items as retention of a metallic lead object in the stomach or an improperly lead-glazed food or beverage container, the child can be promptly separated from the source. Such is not the case when lead paint in the home is the principal source. Several methods are used to remove old lead-based paint from walls and woodwork. Some methods, particularly removal by burning and sanding, greatly increase the amount of air and dustborne lead in the home. Very fine lead-bearing particulates settle out slowly over many hours after burning and sanding is completed. *It is of the utmost importance to remove all young children and pregnant women from a dwelling until the abatement process is completed. They should live elsewhere day and night,* and should not return until removal of all lead-bearing paint has been completed and the dwelling has been thoroughly vacuumed and scrubbed with high-phosphate-detergent solutions. The sources that have been denuded during the abatement process should be repainted to seal any residual lead behind the surface. Children should be removed from the home during abatement whether or not they have increased lead absorption. When this procedure is not followed, it is not uncommon to observe 30 to 50 μg/dl increments in whole blood lead concentration within a matter of a few days or weeks.

Long-range dust control. *It must be understood that dust control is not a substitute for abatement.* In areas heavily contaminated with lead, such as deteriorating old housing and dwellings adjacent to lead-emitting industrial plants or heavy vehicular traffic, it may be helpful to institute a regular program in and about the home to control lead-bearing dust, which constantly reaccumulates. Because hand-to-mouth activity is common in young children, parents must institute a specific type of cleaning program; vacuuming and wet cleaning are recommended. Sweeping with a broom, although it may remove large fragments, serves only to stir up smaller particulates. It is recommended that all floors and woodwork be scrubbed weekly with high-phosphate detergents such as Tide or Spic and Span. For all surfaces that the child can touch, the weekly scrubbing should be supplemented with daily damp dusting with a cloth rinsed in a solution of high-phosphate detergent. Although such cleaning programs may be helpful, the definitive way to prevent recurrences is for affected children and their families to move into housing free of lead paint hazards.

Dietary factors. Although reduction in exposure to environmental lead must receive first priority, steps should be taken to identify and correct deficient dietary intake, particularly of calcium[25, 35] and iron as well as excessive dietary fat, each of which may increase the absorption and retention of lead. A diet adequate in minerals and limited in fat should be assured. For those intolerant of cow milk, lactose-free milk products such as yogurt or some alternative source are necessary to ensure adequate calcium intake. The use of low-fat milk and the avoidance of fried foods should limit excessive dietary fat. Acidic foods such as fruits, fruit juices, tomatoes, sodas, and cola drinks may

leach lead from cans with leaded-soldered seams. Dietary lead intake may be reduced if the above items are purchased fresh, frozen, or packaged in aluminum, glass, cardboard, or plastic containers.

Neurobehavioral considerations. A major problem is presented by the high level of hand-to-mouth activity of many preschool-aged children. If hand-to-mouth activity or pica (ingestion of nonfood items) is particularly severe, a behavioral psychologist can be helpful in developing a program to reduce the activity.

For children given any combination of chelating agents, neurologic and psychologic assessment should be obtained at the time of initial diagnosis and during the following years. This will facilitate appropriate school placement for children with learning handicaps, if they are identified through thorough psychometric evaluation prior to the child's entry into the school system. For the child who has had acute lead encephalopathy, long-term anticonvulsant therapy with phenytoin (or phenobarbital) is indicated if there were seizures or coma during the encephalopathic episode. Additional clinical and laboratory evaluation may be indicated to detect other sequelae of chronic lead poisoning, such as renal impairment. Metabolic disorders associated with acute lead poisoning are reversible after chelation therapy and substantial reduction of lead exposure.

Frequency of follow-up. When the results of initial venous blood lead and EP values and CaNa2-EDTA testing indicate the need for chelation therapy, long-term follow-up is indicated. For those children who have not received chelation therapy, follow-up at 3-month intervals, together with abatement and dust control in the home and correction of dietary deficiencies, should be continued until the child has maintained normal blood lead and EP values for 1 year.

Those children who initially received a course of chelation therapy require more intensive follow-up. Abatement of environmental lead hazards in the home is rarely accomplished within a matter of a few days, so that as a general rule the first course of chelation therapy is given in the hospital. Outpatient chelation therapy while a child is still overexposed to lead is counterproductive and likely to be associated with enhanced absorption and retention of lead. In children who have received a course of chelation therapy, blood lead and EP determinations should be repeated 5 to 7 days after therapy and then after another 1 to 4 weeks, depending on the progress. If some improvement is observed, follow-up may be scheduled at 2- to 4-week intervals for 6 months. Thereafter, blood lead and EP tests should be repeated at 3-month intervals until the child is 6 years of age. At each visit the environmental and housing situations are updated and reevaluated and dust

control and diet are reviewed. If serial blood lead and EP data show continued improvement, it may be assumed that new assimilation of new lead is not occurring; rising blood lead concentrations, which may be followed by a rising EP level, indicate increased ingestion of lead. Often, reinvestigation reveals new sources of environmental lead not previously detected. When a child with earlier elevated blood lead concentrations approaches school age, psychometric evaluation may be indicated, even though the blood lead concentration at the time is <25 μg/dl.

Summary. Increased body lead burden must be managed as a chronic disorder. The final evaluation and disposition of each case must take into account the entire prior record. It is prudent to observe mentally or developmentally handicapped children with persistent pica during school years, because recurrences after the age of 6 years are most likely to occur in these children. The need to remove infants, young children, and pregnant women from a home during abatement of lead paint hazards is crucial to prevent acute episodes of sharply increased lead toxicity.

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